Applicants reserve their right to pursue these claims in a continuation application.

Claims 32 and 33 have been withdrawn from consideration by the Examiner as directed to a non-elected invention. Applicants herein traverse the holding of Lack of Unity of Invention. In the event that the Lack of Unity of Invention is maintained, Applicants reserve the right to pursue the subject matter of the unexamined claims in a divisional application.

The claims have been amended in order to more particularly point out and distinctly claim what Applicants regard as their invention. Support for these amendments may be found in the claims as originally filed. No new matter has been added.

Summary of the Examiner's Office Action

The Office action dated January 21, 1998 contains the following:

(1) Requirement for election on the basis of Lack of Unity of Invention Under PCT Rule 13.1;
(2) Requirement to amend the Specification by claiming benefit of an earlier application;
(3) Discussion of the Information Disclosure Statement;
(4) Requirement to correct the Specification under 37 CFR 1.75(d)(1);
(5) Objection to the claims;
(6) Rejection of claims 48-55 under 35 U.S.C. 101;
(7) Rejection of Claims 27-31 and 34-55 Under Section 112, First Paragraph;
(8) Second Rejection of Claims 27-31 and 34-55 Under Section 112, First Paragraph;
(9) Rejection of Claims 29, 35-39, 43 and 53 Under Section 112, Second Paragraph;
(10) Rejection of Claims 27, 28, 30, 31, 34-39, 41 and 48-50 Under Section 102(b)/103(a);
(11) Rejection of Claims 27, 28, 30, 31, 34-36, 39-41 and 48-50 Under Section 102(e)/103(a);
(12) Rejection of Claims 36-38 and 50 Under Section 102(b)/103(a).

Each of the issues raised by the Examiner are discussed below. Applicants believe that the foregoing amendment and the following remarks

respond completely to the objections and rejections. Applicants further believe the claims are in condition for allowance.

(1) Requirement for election on the basis of Lack of Unity of Invention Under PCT Rule 13.1

The Examiner has required election of one of the following groups of claims on the Basis of Lack of Unity of Invention Under PCT Rule 13.1:

Group I, claims 27-31 and 34-55, directed to adenoviruses comprising a glutathione peroxidase gene;

Group II, claims 32-33, directed to adenoviruses comprising a sequence encoding an antisense against glutathione peroxidase.

During a telephone conversation on December 8, 1997, Applicants provisionally elected Group I, with traverse. Applicants affirm this provisional election with traverse, but respectfully request reconsideration and modification of the finding of lack of unity with respect to the claims of Group I and Group II.

Applicants submit that the claims of Group I and Group II are so linked as to form a single general inventive concept. The claims of Group I include subject matter directed to an adenovirus encoding a glutathione peroxidase. The claims of Group II are directed to an adenovirus encoding an antisense sequence against glutathione peroxidase. The claims of Group II share special technical features with adenovirus of Group I. Group I and Group II are, therefore, linked as to form a single general inventive concept under 37 CFR § 1.475.

Applicants further submit that examination of the claims of Group I and Group II together would not impose an undue burden on the Examiner. An exhaustive search for an adenovirus encoding glutathione peroxidase would encompass the art disclosing related adenoviruses encoding the corresponding antisense sequence. Similarly, a search for a particular antisense sequence would necessarily reveal information about the nucleic acid sequence to which it hybridizes. Indeed, performing the entire search covering both the nucleic acid sequence and its related antisense sequence is less burdensome on the Examiner than the separate search, which necessarily involves duplication of searching efforts.

In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the finding of lack of unity between the claims of Group I and Group II.

(2) Requirement to Amend the Specification by Claiming Benefit of an Earlier Application

The Examiner has required an amendment to the Specification, stating that the present application is a 371 of an international application. Applicants have amended the Specification accordingly.

(3) Discussion of the Information Disclosure Statement

The Examiner has stated that reference PD (Danos et al.) of the Information Disclosure Statement filed March 6, 1997, has not been considered because 1) it is not in the English language; and 2) a concise explanation of the relevance of this document was not provided. Applicants submit respectfully that the Information Disclosure Statement complies with 37 CFR 1.98(a)(3), and that the reference of Danos et al. should properly be considered by the Examiner.

As stated in the Information Disclosure Statement

> Publication PD is in the French language. As a concise explanation of the relevance of Publication PD as it is (sic) presently understood, Applicants submit herewith: (1) an English translation of the International Search Report (Appendix 1), showing the relevance found by the International Search Authority; and (2) an English language translation of Section V of the International Preliminary Examination Report (Appendix 2), showing the relevance found by the International Preliminary Examination Authority.

Applicants submit respectfully that this is all that is required to meet the requirements of 37 CFR 1.98(a)(3).

(4) Requirement to correct the Specification under 37 CFR 1.75(d)(1)

The Examiner has stated that there is no antecedent basis in the specification for the term respiratory distress syndrome (ADRS), as recited in claim 43. In response, Applicants direct the Examiner's attention to page 12,

lines 2-3, and submit that no further amendment to the specification is necessary.

(5) Objection to the claims

The Examiner has objected to the language of claims 28-31, 34-42, 45-47, 49, 50, and 52-55. In response, Applicants have amended the claims according to the Examiner's suggestions.

(6) Rejection of claims 48-55 under 35 U.S.C. 101

Claims 48-55 stand rejected under 35 USC § 101, as directed to nonstatutory subject matter. Applicants respectfully traverse this rejection. Claim 48 defines a cell infected with a defective, recombinant adenovirus. Such cells are not a product of nature. In the Examiner's view the claims

> read on cells and implants present in a human subject wherein the host cells are either part of the human or were derived from that subject before being implanted back into the human subject. Thus the claims (sic) in essence read upon an integral part of the human subject or the subject as a whole, which is non-statutory subject matter

(Office action at pages 5-6). Applicants respectfully disagree with the Examiner's conclusion. According to the MPEP

> If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to non-statutory subject matter

(MPEP 2105). Applicants submit respectfully that it is not reasonable to interpret claims 48-55, which are directed to cells and implants, as encompassing a human being. Furthermore, Applicants are aware of numerous issued US patents which claim mammalian cells, and are prepared to make these of record if necessary. Accordingly, Applicants request respectfully that this rejection may be properly withdrawn.

(7) Rejection of Claims 27-31 and 34-55 Under Section 112, First Paragraph

Claims 27-31 and 34-55 stand rejected under 35 USC § 112, first paragraph as not adequately described in the specification. In particular, the Examiner has objected to the breadth of the claims with respect to glutathione peroxidase. The Examiner has also objected to the terms MLP, CMV, and RSV-LTR promoters. Applicants respectfully traverse this rejection, and submit that the specification contains a disclosure of the claimed invention which meets the requirements of 35 USC § 112, first paragraph.

The proper test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 188 USPQ 659 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent Inc.* 3 USPQ2d 1737 (Fed. Cir. 1987). In this case the structure of various glutathione peroxidase genes, and of the MLP, CMV, and RSV-LTR promoters, are well known in the art.

Various DNAs encoding glutathione peroxidases are described on pages 4-5 of the specification. In particular, the reference of Mullenbach et al. (cited on page 5, line 3) provides the cDNA sequences for pituitary, kidney and placental glutathione peroxidases from bovine, human and mouse sources, respectively (see page 313 and Figure 1). In addition, numerous references describing glutathione peroxidase types GPX1, GPX2, GPX3 and GPX4 are cited and discussed on page 4, lines 5-20, of Applicants' specification. Applicants submit that one skilled in this art could, based on this disclosure, make and use a recombinant adenovirus comprising a DNA sequence encoding a glutathione peroxidase, the subject matter of the claimed invention.

With respect to the terms MLP, CMV, and RSV-LTR promoters, Applicants submit that these are terms that are well known and understood in the art. As evidence thereof, Applicants direct the Examiner's attention to WO 94/08026, which was cited by the Examiner on PTO Form 892. WO 94/08026, like the present application, is directed to gene therapy, particularly of disorders of the central nervous system using replication defective adenoviruses. Therefore, WO 94/08026 constitutes subject matter known to those skilled in the art of the invention claimed herein. Each of the terms MLP, CMV, and RSV-

LTR are defined in this international application. Page 4, lines 18-19 defines MLP as the major late promoter of a human adenovirus. Similarly, RSV-LTR is defined as the Rous Sarcoma virus long terminal repeat (see page 4, lines 27-28 and page 10, lines 12-13). CMV represents a promoter derived from cytomegalovirus (page 4, line 29). Applicants submit respectfully that WO 94/08026 is evidence that each of the terms MLP, CMV, and RSV-LTR would be understood by anyone skilled in the relevant art.

(8) Second Rejection of Claims 27-31 and 34-55 Under Section 112, First Paragraph

Claims 27-31 and 34-55 stand rejected under 35 USC § 112, first paragraph. Applicants respectfully traverse this rejection, and submit that the claims are enabled by their Specification and meet each of the requirements of 35 U.S.C. 112, first paragraph. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

Applicants believe that the above amendments to the claims address most of the issues raised by the Examiner (see pages 8-16 of the Office action). In particular, claims 42 and 43 have been canceled. Therefore, the rejection is moot with respect to these claims. Solely in an effort to advance prosecution independent claim 27 has been amended by removing reference to "an active part" or to derivatives of glutathione peroxidase. For the reasons discussed in Section 7, above, Applicants believe that further limitation of the claims to particular glutathione peroxidases, as suggested by the Examiner, would unduly limit the scope of protection to which Applicants are entitled. Applicants also believe that the terms MLP, CMV and RSV-LTR are definite and clear, and would be understood by anyone skilled in this art (see the discussions in section 7, above, and in section 9, below).

The Examiner has also suggested that the claims be limited to particular strains of adenovirus. Applicants respectfully traverse this aspect of the rejection. The types of adenovirus suitable for practice of this invention are clearly described in the specification (see page 9, line 19, through page 10, line 7). These include human adenoviruses type Ad2 and Ad5, as well as various animal adenoviruses. The animal adenoviruses may be of canine, bovine, ovine, murine, porcine, avian, or simian origin. Preferably, the animal adenovirus is a canine CAV2 adenovirus. Animal adenoviruses are discussed further in French patent application FR93 05954 entitled "Adenoviral Vectors of Animal Origin and Use Thereof in Gene Therapy" (cited on page 9, line 23 in the

present application). If necessary, Applicants are prepared to submit an English translation of WO 94/26914, the international application corresponding to FR93 05954.

Contrary to the Examiner's suggestion on page 9, pharmaceutical compositions and implants comprising recombinant adenoviruses have been shown to be efficacious *in vivo*. In particular, the genetic engineering of mammalian cells to express a therapeutic gene, and subsequent implantation of these cells into the CNS of a patient to produce a beneficial effect is enabled.

Applicants submit herewith copies of issued U.S. patents 5,082,670 and 5,560,148 (attached hereto as Exhibits A and B, respectively). These patents disclose and claim methods of treating CNS disorders by grafting genetically modified cells into the CNS of a patient. In particular, these issued patents claim infection of cells with a virus carrying a therapeutic transgene, and implanting these cells into the CNS of a patient in order to treat defective, diseased or damaged CNS cells.

The link between free radicals, hydroxyl radicals in particular, and various diseases, including neurological disorders, is discussed on pages 1-2 of the present application. Glutathione peroxidase is an enzyme capable of regulating free radical levels and, thereby, of treating these disorders. Applicants have demonstrated that an adenovirus encoding glutathione peroxidase is capable of directing the expression of glutathione peroxidase in mammalian cells (see Example 3). U.S. patents 5,082,670 and 5,560,148 are evidence that such mammalian cells upon implantation into a patient would reasonably be expected to effect free radical concentrations in the patient. Specifically, the claims of an issued US patent carry a presumption of validity. Applicants submit respectfully that these patents are compelling evidence supporting the efficacy of the claimed compositions and implants comprising genetically modified cells expressing glutathione peroxidase.

(9) Rejection of Claims 29, 35-39, 43 and 53 Under Section 112, Second Paragraph

Claims 29, 35-39, 43 and 53 stand rejected under 35 USC § 112, second paragraph. Claims 39 and 43 have been cancelled. Therefore, the rejection is moot with respect to these claims. Claims 29, 35-38 and 53 have been amended in order to more particularly point our and distinctly claim what Applicants regard as their invention. In particular, the claims have been

amended for clarity, and to provide proper antecedent basis for each of the limitations of the claims.

With respect to claims 36-38, Applicants submit that each of the terms E1A, MLP, CMV and RSV-LTR are definite and clear, and would be understood by one skilled in the art. As discussed above, each of the terms MLP, CMV and RSV-LTR are art recognized terms for promoters known to be useful in constructing replication defective adenoviral vectors, the subject matter of the claimed invention. WO 94/08026 is evidence of this fact. Applicants believe that further definition or clarification of these terms is, therefore, unnecessary.

With regard to the E1A promoter the Examiner himself has admitted that

> this indicates a known structure evident from the specification as being the endogenous adenovirus promoter of the E1a region

(Office action at page 7). This well known promoter is also discussed in WO 94/08026 (see page 4, lines 20-24). Therefore, Applicants believe that the metes and bounds of this term would also be understood by the skilled artisan.

Applicants submit respectfully that the claims are both definite and clear and meet the requirements of 35 USC § 112, second paragraph. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(10) Rejection of Claims 27, 28, 30, 31, 34-39, 41 and 48-50 Under Section 102(b)/103(a)

Claims 27, 28, 30, 31, 34-39, 41 and 48-50 stand rejected under 35 USC § 102(b)/103(a) as unpatentable over Kahn et al. in view of Mullenbach et al. Claim 39 has been cancelled. Therefore, the rejection is moot with respect to this claim. Applicants respectfully traverse this rejection with respect to the remaining claims. This combination of references in no way teaches or suggests Applicants invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Kahn et al.

Kahn et al. disclose replication defective adenoviruses for the transfer of genes into cells of the central nervous system. Kahn et al. disclose a number of genes encoding therapeutic molecules, which may be incorporated into the adenovirus, including antisense sequences, neurotransmitter synthesizing enzymes, growth factors, and neurotrophic factors.

Kahn et al. does not teach a replication defective recombinant adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase.

Mullenbach et al.

Mullenbach et al. discloses the cDNA sequences for pituitary, kidney and placental glutathione peroxidases from bovine, human and mouse sources, respectively (see page 313 and Figure 1).

Mullenbach et al. neither teach nor suggest replication defective adenoviruses. Mullenbach et al. certainly do not teach a replication defective recombinant adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase.

(b) Kahn et al. Do Not Render Obvious the Claimed Invention

Applicants' independent claim 27 defines a replication defective recombinant adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase. Kahn et al. neither teach nor suggest the invention defined by claim 27. The reference is deficient because it fails to teach or suggest a DNA sequence encoding a glutathione peroxidase, and a defective recombinant adenovirus comprising such a DNA sequence. Absent such a disclosure, Kahn et al., either alone or in combination with Mullenbach et al., cannot possibly render *prima facie* obvious the invention defined by Applicants' claim 27, or any of the claims which are dependent thereon.

(c) Mullenbach et al. do not correct the deficiencies of Kahn et al.

Obviousness under Section 103 is a question of law. Panduit Corp. v. Dennison Mfg. Co., 1 USPQ2d 1593, 1597 (Fed. Cir.), cert denied, 481 U.S. 1052 (1987). "Both the suggestion and the expectation of success must be founded in the prior art, not in Applicants' disclosure." In re Dow Chemical Company, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The burden of establishing a *prima facie* case of obviousness resides with the PTO. In re Piasecki, 223 USPQ 785, 788 (Fed. Cir. 1984) (quoting In re Warner, 154 USPQ 173, 177 (CCPA 1967)). However, nothing in the art cited by the Examiner teaches or suggests each of the recited elements of Applicants claimed invention. Specifically, none of the cited references teach or suggest a replication defective recombinant adenovirus encoding glutathione peroxidase. Mullenbach et al. is limited to a disclosure of DNA sequences encoding various glutathione peroxidases. Therefore, Mullenbach et al. cannot possibly correct the deficiencies of Kahn et al., because neither reference teaches or suggests insertion of a DNA sequence encoding glutathione peroxidase into a replication defective recombinant adenovirus. Applicants were the first to make this invention, and to propose its use for the treatment and/or prevention of diseases, including neurodegenerative disease.

The Examiner is clearly picking and choosing from various teachings in the cited references in an effort to reconstruct the claimed invention. However,

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Wesslau, 147 USPQ 391, 393 (CCPA 1965). In this case the primary reference, Kahn et al., fails to suggest an adenovirus vector encoding a glutathione peroxidase. Mullenbach et al. suggest nothing beyond a sequence encoding this enzyme. Indeed, nothing in the art cited by the Examiner teaches or suggests a replication defective adenovirus comprising a sequence encoding glutathione peroxidase, the subject matter of the claimed invention.

At best, the Examiner's position poses an "obvious to try" situation. However, the Federal Circuit Court has, on numerous occasions, noted that while something may be obvious to try, it may not be obvious under 35 U.S.C. § 103. The proper standard is whether the prior art would have suggested to one

of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. *In re Dow Chemical Company*, 5 USPQ 2d 1529, 1531 (Federal Circuit, 1988).

> Both the suggestion and the expectation of success must be founded in the prior art, not in Applicants' disclosure. Id.

In this case the combination of Kahn et al. with Mullenbach et al. simply does not suggest to one of ordinary skill in the art that Applicants' claimed invention could be achieved with a reasonable likelihood of success. Accordingly, the rejection must be based on improper hindsight given the benefit of Applicants' disclosure. However, use of hindsight reconstruction of an invention using Applicant's teachings is clearly improper, as has been stated by The Court of Appeals for the Federal Circuit on many occasions,

> "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."

W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ at 312-313 (Federal Circuit, 1983).

> "Those charged with determining compliance with 35 U.S.C. §103 are required to place themselves in the minds of those of ordinary skill in the relevant art at the time the invention was made, to determine whether that which is now plainly at hand would have been obvious at such earlier time.
> The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."

Interconnect Planning Corporation v. Feil, et al., 227 USPQ at 547 (Federal Circuit, 1985).

In this case, nothing in the art cited by the Examiner teaches or suggests a replication defective recombinant adenovirus encoding glutathione peroxidase, or its use for the treatment of neurodegenerative diseases. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(11) Rejection of Claims 27, 28, 30, 31, 34-36, 39-41 and 48-50 Under Section 102(e)/103(a)

Claims 27, 28, 30, 31, 34-36, 39-41 and 48-50 stand rejected under 35 USC § 102(b)/103(a) as unpatentable over McClelland et al. in view of Mullenbach et al. Claim 39 has been cancelled. Therefore, the rejection is moot with respect to this claim. Applicants respectfully traverse this rejection with respect to the remaining claims. This combination of references in no way teaches or suggests Applicants invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

McClelland et al. disclose a modified adenovirus in which a portion of the viral fiber protein is replaced with a cell specific ligand. McClelland et al. teach that the adenovirus may also encode a therapeutic agent, and provides a list of potential DNA sequences for insertion into the vector.

Significantly, McClelland et al. neither teaches nor suggests glutathione peroxidase as a therapeutic agent. McClelland et al. certainly does not teach a replication defective recombinant adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase, the subject matter of the claimed invention.

Mullenbach et al. fail to correct the deficiencies of McClelland et al. As discussed above, Mullenbach et al. merely disclose the cDNA sequences for various glutathione peroxidases. However, Mullenbach et al. neither teach nor suggest replication defective adenoviruses. Neither does the reference suggest a replication defective recombinant adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase. Absent such a disclosure, McClelland et al., either alone or in combination with Mullenbach et al., cannot possibly render *prima facie* obvious the invention defined by any of Applicants' claims. Applicants were the first to suggest the adenoviruses claimed herein, and to propose their use for the treatment and/or prevention of neurodegenerative diseases. As above, the combination of McClelland et al. with Mullenbach et al. is only possible using improper hindsight based on Applicants' disclosure. Accordingly, this rejection is untenable and should be withdrawn.

(12) Rejection of Claims 36-38 and 50 Under Section 102(b)/103(a)

Claims 36-38 and 50 stand rejected under 35 USC § 102(b)/103(a) as unpatentable over McClelland et al. in view of Mullenbach et al., and further in view of Akli et al. Applicants respectfully traverse this rejection. For the reasons discussed above, his combination of references also fails to teach or suggest Applicants invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

Akli et al. disclose the transfer of foreign genes into the brain using adenovirus vectors. In particular, Akli et al. teach the infection of a population of brain cells with an adenovirus encoding an *E. coli* lacZ marker gene, and expression of the gene in the brain for up to 45 days.

Akli et al. fail to correct the deficiencies of McClelland et al. and Mullenbach et al. Akli et al. neither teach nor suggest a replication defective adenovirus comprising at least one DNA sequence encoding a glutathione peroxidase. Absent such a disclosure, Akli et al., either alone or in combination with McClelland et al. and Mullenbach et al., cannot possibly render *prima facie* obvious the invention defined by any of Applicants' claims. Indeed, none of the references cited by the Examiner, either explicitly or implicitly, teach or suggest the invention defined by the present claims. Accordingly, Applicants submit respectfully that this rejection is improper and should be withdrawn.

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicant's attorney invites the Examiner to contact Paul Fehlner at (610) 454-3839.

Respectfully submitted,

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Dated: 21 July 1998

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